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Fatty Nitrogen Derived Amides High Production Volume (HPV) Chemicals Challenge

Test Plan

Prepared for:

American Chemistry Council
Fatty Nitrogen Derivatives Panel
Amides Task Group

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Fatty Nitrogen Derived Amides
High Production Volume (HPV) Chemicals Challenge
Test Plan

This document provides the Test Plan for the Fatty Nitrogen Derived Amides Chemical Category.

Definition of Fatty Nitrogen Derived (FND) Amides Structure-Based Chemical Category and Subcategories

The FND Amides Chemical Category is comprised of 29 separate chemicals with unique CAS Registry Numbers (RNs). To facilitate the evaluation, interpretation and comparisons of available data for SIDS/HPV endpoints, the category was divided into the following four subcategories:

Subcategory I:	Substituted Amides
Subcategory II:	Fatty Acid Reaction Products with Amino Compounds (Note: Subcategory II chemicals, in many cases, contain Subcategory I chemicals as major components)
Subcategory III:	Imidazole Derivatives
Subcategory IV:	FND Amphoterics

Subcategory I includes 12 substituted amides and Subcategory II includes 9 fatty acid amides reacted with amino compounds. Subcategory III represents five heterocyclic imidazole chemicals and Subcategory IV represents three amphoteric amides.

In addition, six non-HPV chemicals, which are structurally related to the category, were identified as supporting chemicals by the American Chemistry Council (ACC) FND Panel, Amides Task Group to provide additional data for the category (two chemicals in Subcategory I, one chemical in Subcategory II, one chemical in Subcategory III, and two chemicals in Subcategory IV). Information for these supporting chemicals is included in the table below and throughout the discussion.

Compositional Information for the FND Amides HPV and Supporting Chemicals

The FND Amides chemicals are identified in the following table:

Text Table A: CAS Registry Numbers and Chemical Names

CAS RN	Chemical Name
Subcategory I – Substituted Amides	
142-78-9	Dodecanamide, N-(2-hydroxyethyl)-
120-40-1	Dodecanamide, N,N-bis(2-hydroxyethyl)-
68155-06-6	*Amides, C12-18, N,N-bis(hydroxyethyl)*
61790-31-6	*Amides, tallow, hydrogenated*
124-26-5	Stearamide
110-30-5	Octadecanamide, N,N'-ethylenebis
68140-00-1	Amides, coco, N-(hydroxyethyl)
68603-42-9	Amides, coco, N,N-bis(hydroxyethyl)
68140-01-2	Amides, coco, N-[3-(dimethylamino)propyl]
301-02-0	Oleamide
93-83-4	Oleamide, N,N-bis(2-hydroxyethyl)-
68155-20-4	Amides, tall-oil fatty, N,N-bis(hydroxyethyl)
68425-47-8	Amides, soya, N,N-bis(hydroxyethyl)
112-84-5	Erucamide

Note: Chemicals in italics are supporting chemicals [non-HPV].

Text Table A: CAS Registry Numbers and Chemical Names (continued)

CAS RN	Chemical Name
Subcategory II – Fatty Acid Reaction Products with Amino Compounds	
68131-13-5	Naphthenic acids, reaction products with diethylenetriamine
8051-30-7	Coconut oil, reaction products with diethanolamine
61790-63-4	Fatty acids, coco, compounds with diethanolamine
61790-69-0	Fatty acids, tall-oil, reaction with diethylenetriamine
68132-46-7	Fatty acids, tall oil, compounds, with triethanolamine
68910-93-0	Fatty acids, tall-oil, reaction products with polyethylenepolyamines
64754-93-4	Fatty acids, tall-oil, reaction products with polyethylenepolyamines, acetates (essentially acetates of CAS RN 68910-93-0)
68910-87-2	*Fatty acids, tall-oil, reaction products with polyalkylenepolyamines, dodecylbenzenesulfonates*
68953-36-6	Fatty acids, tall-oil, reaction products with tetraethylenepentamine
71820-35-4	Fatty acids, tall-oil, low boiling, reaction products with 1-piperazineethanamine
Subcategory III – Imidazole Derivatives	
68122-86-1	*Imidazolium compounds, 4,5-dihydro-1-methyl-2-nortallow alkyl-1-(2-tallow amidoethyl) Me sulfate*
61791-39-7	1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-nortall-oil alkyl derivatives
68442-97-7	1H-Imidazole-1-ethanamine, 4,5-dihydro-, 2-nortall-oil alkyl derivatives
72623-72-4	Amides, C14-18, N-[2-(C13-17-alkyl-4,5-dihydro-1H-imidazol-1-yl)ethyl]
72749-55-4	Imidazolium cmpds., 2-(C17 & C17-unsatd. Alkyl)-1[2-(C18 & C18-unsatd. amido) ethyl]-4,5-dihydro-1-methyl, Me sulfates
65817-50-7	1,2-Ethanediamine, N-(2-aminoethyl)-N'-{2-(8Z)-8-heptadecenyl-4,5-dihydro-1H-imidazol-1-yl}ethyl

Note: Chemicals in italics are supporting chemicals [non-HPV].

Text Table A: CAS Registry Numbers and Chemical Names (continued)

CAS RN	Chemical Name
Subcategory IV – FND Amphoterics	
693-33-4	Ammonium, (carboxymethyl)hexadecyldimethyl-, hydroxide, inner salt
4292-10-8	*1-Propanaminium, N-(carboxymethyl)-N,N-dimethyl-3-[(1-oxododecyl)amino]-, inner salt*
61789-39-7	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-dimethyl-, N-coco acyl derivatives, chlorides, sodium salts
61789-40-0	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivatives, inner salt
70851-07-9	*Amides, coco, N-[3-(dimethylamino)propyl], alkylation products with chloroacetic acid, sodium salts*

Note: Chemicals in italics are supporting chemicals [non-HPV].

Evaluation of Matrix Data Patterns – Reliable Data and QSAR Predictions

Physical/Chemical Properties

Robust summaries for the reliable studies are provided in Appendix A.

Melting Point, Boiling Point and Vapor Pressure: Melting point and boiling point data as predictors of environmental or toxicological behavior for chemicals such as the FND Amides Category chemicals are of minimal value. The QSAR estimates for melting point and boiling point appear to provide values higher than expected or measured but are within a factor of approximately 4 or less. Overall, for HPV purposes the measured and modeled values are adequate for defining melting and boiling points for the FND Amides Category chemicals.

As expected for molecules of this size, model predictions for the chemicals with definable structures indicate they are nonvolatile. Overall, the available information is adequate to meet HPV requirements.

> **Additional Data:** No additional testing is proposed for the melting point, boiling point and vapor pressure endpoints (see Table 1).

Octanol/Water Partition Coefficient (K_{ow}) and Water Solubility: Predicted or measured K_{ow} values are of limited practical use for the FND Amides Category chemicals. An inherent property of surfactants is that they tend to accumulate at the interface between hydrophobic and hydrophilic phases rather than equilibrate between the two phases. Therefore, the accurate measurement of the K_{ow} of any surfactant is notoriously difficult. Even if such measurements were made accurately, the K_{ow} is not an appropriate value by which to predict the partitioning behavior of the FND Amides Category chemicals in the environment because of the tendency to partition at lipid/aqueous interfaces.

The measured values and company information for water solubility of the FND Amides Category chemicals indicate that the tested chemicals are insoluble. The model predictions, however, range from insoluble to moderately soluble. The physical/chemical properties of surfactants, as described above, often make water solubility data of little practical value in the determination of environmental fate and effects. However, if any of the chemicals in the FND Amides Category are water soluble, the overall predictability of the ultimate fate and effects may be impacted.

> **Additional Data:** Due to the importance of water solubility in the ultimate determination of environmental fate and effects, experimental determination of this parameter is proposed for several chemicals (see Table 1). The chemicals proposed for testing include: CAS RN 142-78-9 from Subcategory I, to establish if the lower molecular weight chemicals in the Subcategory may be soluble when the other chemicals in the subcategory are not and CAS RN 693-33-4 from subcategory IV, to establish the solubility characteristics of the amphoteric salts. Chemicals in Subcategory II are considered insoluble based on the available company literature and the read-across from the insoluble chemicals in Subcategory I. Chemicals in Subcategory III are considered insoluble based on company literature and structure. If the testing indicates that some of the chemicals are water soluble, additional tests may be required to further define soluble and insoluble members of the FND Amides Category.

Environmental Fate and Ecotoxicity

Robust summaries for the reliable studies are provided in Appendix A.

Photodegradation, Water Stability and Fugacity: Due to the low volatility of the FND Amides chemicals, atmospheric photodegradation estimates are of no practical use. However, photodegradation was predicted for the FND Amides Category chemicals that could be modeled. These predictions indicate that these chemicals would be expected to degrade relatively rapidly upon exposure to light ($t_{1/2}$ values ranging from approximately 2.2 to 9.5 hours).

The water stability of these chemicals could not be modeled since the structures of the FND Amides did not meet the requirements of the model's database. Due to the surfactant properties and solubility of the FND Amides, hydrolytic stability is of minimal value for determining environmental fate or effects.

The Level III fugacity model predictions are consistent with the model dependency on K_{ow}. Thus, for the chemicals with lower K_{ow} estimates, the model predicts higher distribution into water while chemicals with higher predicted K_{ow} values have distribution predictions primarily to sediment. As discussed above for water solubility, it is possible that the predictions of substantial distribution to water are overestimated, which can be confirmed with the proposed water solubility testing.

> **Additional Data:** For HPV purposes, model predictions for chemicals with definable structures are adequate for the FND Amides Chemical Category and no additional testing is proposed.

Biodegradability: There are adequate measured data across Subcategories I, II and IV to allow the conclusion that the these chemicals are readily or inherently biodegradable. Further, the model predictions provide reasonably close estimates to these measured values. Minimal degradability of the non-HPV chemical, CAS RN 68122-86-1, from Subcategory III indicates these chemicals are slowly degraded. The slower degradation of these materials is likely the result of the water solubility and behavior of the chemicals in aqueous solution.

Additional Data: No additional testing is proposed for biodegradation (see Table 2).

Aquatic Toxicity: The reliable data for acute toxicity to fish and daphnid indicate that the FND Amides Category chemicals, like surfactants in general, may adversely affect aquatic organisms (LC_{50} and EC_{50} values ranging from 0.2 to 59 mg/l). Many of the ECOSAR model estimates for the acute toxicity endpoints indicate the chemicals are "not toxic at solubility".[1] However, for surfactants such as the FND Amides Category chemicals, the acute aquatic toxicity generally is considered to be related to the effects of the surfactant properties on the organism and not to direct chemical toxicity. Although the model estimates for acute toxicity to fish and daphnid may have limitations, there are adequate reliable data for Subcategories I, III, and IV to establish the acute toxicity of these chemicals to fish and invertebrates. In addition, a single chronic toxicity study with invertebrates (CAS RN 112-84-5) in Subcategory I supports these results. While there are limited direct data for acute aquatic toxicity for Subcategory II chemicals, including a LC_{50} value for fish (CAS RN 68910-93-0) and an EC_{50} value for daphnia (CAS RN 71820-35-4), Subcategory I chemicals are major components of many Subcategory II chemicals. Therefore, for HPV purposes, there is adequate supporting information for Subcategory II chemicals to conclude they have similar toxicity to the other subcategories. Reliable data for acute toxicity to aquatic plants for two of the FND Amides Category chemicals suggest that these chemicals may affect these species adversely. Model predictions are inconsistent and difficult to interpret for this endpoint ranging from "not toxic at solubility" to EC_{50} values of less than 1 ppb for chemicals of similar structure.

[1] Note that in these cases, the model provides an estimated LC_{50} or EC_{50} value but states "chemical may not be soluble enough to measure this predicted effect." The preferred designation of "not toxic at solubility" is used since incorporation of the predicted value that is above the solubility or the use of the caveat as stated in the model provides for greater uncertainty.

Additional Data: The aquatic toxicity of the FND Amides Category chemicals (measured and modeled) are similar to those known for other surfactants. Since acute toxicity to aquatic animals and plants is known to be a measure primarily of physical effects resulting from the surfactant properties of the chemicals, additional testing will not provide new data of consequence. Therefore, no additional data development is proposed (see Table 2). This recommendation should be reevaluated following determination of the water solubility characteristics of some of the chemicals as described above.

Human Health-Related Data

Robust summaries for the reliable studies are provided in Appendix A.

Acute Toxicity: The low acute oral toxicity of the FND Amides Category chemicals is well established across all Subcategories by the available data. The limited acute toxicity of these chemicals is also confirmed by four acute dermal and two acute inhalation studies.

Repeated Dose and Reproductive Toxicity: Two subchronic toxicity studies demonstrating low toxicity are available for Subcategory I chemicals. In addition, a 5-day repeated dose study for a third chemical confirmed the minimal toxicity of these chemicals. Since the Subcategory I chemicals are major components of many Subcategory II chemicals, and based on the low repeat-dose toxicity of the amino compounds (e.g. diethanolamine, triethanolamine) used for producing the Subcategory II derivatives, the Subcategory I repeat-dose toxicity studies adequately support Subcategory II. The two subchronic toxicity studies in Subcategory I adequately evaluated reproductive organs to meet the SIDS/HPV criteria for reproductive screening. Based on the same reasoning as above, these data are considered adequate for Subcategory II. For the non-HPV chemical, CAS RN 68122-86-1, in Subcategory III, a comprehensive subchronic study in dogs and an older subchronic study in rats were available. Both studies confirmed the low order of repeat dose toxicity for the FND Amides Imidazole derivatives. The dog study met the criteria for SIDS/HPV reproductive screening. For Subcategory IV, two subchronic toxicity studies for one of the HPV chemicals indicated a low order of repeat-dose toxicity for the FND amphoteric salts similar to that seen in the other categories. Both of these studies met the criteria for HPV reproductive screening.

Genetic Toxicity *in vitro*: Based on the lack of effect of one or more chemicals in each subcategory, adequate data for mutagenic activity as measured by the *Salmonella* reverse mutation assay exist for all of the subcategories. A chromosomal aberration assay was available for only the non-HPV chemical, CAS RN 68122-86-1, in Subcategory III. A determination of chromosomal aberrations in mammalian cells is required under the SIDS/HPV program.

Developmental Toxicity: A developmental toxicity study in Subcategory I (CAS RN 68603-42-9) and in Subcategory IV (CAS RN 693-33-4) for HPV chemicals and a third study for a non-HPV chemical in Subcategory III (CAS RN 68122-86-1) are available. The studies indicate these chemicals are not developmental toxicants, as expected based on their structures, molecular weights, physical properties and knowledge of similar chemicals. In Subcategory I, CAS RNs 68155-06-6 (C12-18) and 68603-42-9, are very similar chemicals, (i.e. coconut oil contains primarily C8-16) and the developmental toxicity study is considered to represent both compounds. Further, since CAS RN 120-40-1 of fixed chain length (C12) is a major component (44 – 53%) of these two mixed chain length compounds, the developmental toxicity potential of CAS RN 120-40-1 is addressed adequately by the developmental toxicity study for CAS RN 68603-42-9. As above for repeat-dose toxicity, the data for Subcategory I are adequate to support Subcategory II.

Additional Data: A determination of chromosomal aberrations in mammalian cells is required under the SIDS/HPV program. The *in vitro* chromosomal assay (OECD 473) is acceptable to meet this requirement, and conduct of this assay is proposed for one chemical in each of Subcategories I, II and IV (Table 3).

Table 1

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Physical/Chemical Properties

CAS RN	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
Subcategory I: Substituted Amides					
142-78-9	A	A	A	A	OECD 105
120-40-1	A	A	A	A	A
68155-06-6	*A*	*A*	*A*	*A*	*A*
61790-31-6	*C*	*C*	*C*	*C*	*C*
124-26-5	A	A	A	A	A
110-30-5	A	A	A	A	A
68140-00-1	C	C	C	C	C
68603-42-9	C	C	C	C	C
68140-01-2	C	C	C	C	C
301-02-0	A	A	A	A	A
93-83-4	A	A	A	A	A
68155-20-4	C	C	C	C	C
68425-47-8	C	C	C	C	C
112-84-5	A	A	A	A	A

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data or proposed testing.
A = Endpoint fulfilled by adequate reliable data or model data.
OECD = Specified test guideline for proposed study.
C = Endpoint fulfilled by category read-across from existing or proposed test data.

Table 1 (continued)

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Physical/Chemical Properties

CAS RN	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
Subcategory II – Fatty Acid Reaction Products with Amino Compounds					
68131-13-5	C	C	C	C	C
8051-30-7	C	C	C	C	C
61790-63-4	C	C	C	C	C
61790-69-0	C	C	C	C	C
68132-46-7	C	C	C	C	C
68910-93-0	C	C	C	C	C
64754-93-4	C	C	C	C	C
68910-87-2	*C*	*C*	*C*	*C*	*C*
68953-36-6	C	C	C	C	C
71820-35-4	C	C	C	C	C

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
A = Endpoint fulfilled by adequate reliable data or model data.
C = Endpoint fulfilled by category read-across from existing or proposed test data.

Table 1 (continued)

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Physical/Chemical Properties

CAS RN	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
Subcategory III – Imidazole Derivatives					
68122-86-1	*C*	*C*	*C*	*C*	*C*
61791-39-7	C	C	C	C	C
68442-97-7	C	C	C	C	C
72623-72-4	C	C	C	C	C
72749-55-4	C	C	C	C	C
65817-50-7	C	C	C	C	C
Subcategory IV – FND Amphoterics					
693-33-4	A	A	A	A	OECD 105
4292-10-8	*C*	*C*	*C*	*C*	*C*
61789-39-7	C	C	C	C	C
61789-40-0	C	C	C	C	C
70851-07-9	*C*	*C*	*C*	*C*	*C*

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data or proposed testing.
A = Endpoint fulfilled by adequate reliable data or model data.
OECD = Specified test guideline for proposed study.
C = Endpoint fulfilled by category read-across from existing or proposed test data.

Table 2

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Environmental Fate and Ecotoxicity

CAS RN	Photo-degradation	Stability in Water	Transport & Distribution	Biodeg-radation	Acute/Prolonged Toxicity to Fish	Acute Toxicity to Inverte-brates	Acute Tox. to Aquatic Plants	Chronic Tox. to Aquatic Invertebrates
Subcategory I: Substituted Amides								
142-78-9	A	NC	A	A	A	A	A	
120-40-1	A	NC	A	A	A	A	A	
68155-06-6	*A*	*NC*	*A*	*A*	*A*	*A*	*A*	
61790-31-6	*C*	*C*	*C*	*A*	*C*	*C*	*C*	
124-26-5	A	NC	A	A	A	A	A	
110-30-5	A	NC	A	A	A	A	A	
68140-00-1	C	C	C	A	A	A	A	
68603-42-9	C	C	C	A	A	A	C	
68140-01-2	C	C	C	C	C	C	C	
301-02-0	A	NC	A	A	A	A	A	
93-83-4	A	NC	A	A	A	A	A	
68155-20-4	C	C	C	C	C	C	C	
68425-47-8	C	C	C	C	C	C	C	
112-84-5	A	NC	A	A	A	A	A	A

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data
A = Endpoint fulfilled by adequate reliable data or model data.
C = Endpoint fulfilled by category read-across from existing or proposed test data.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

Table 2 (continued)

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Environmental Fate and Ecotoxicity

CAS RN	Photo-degradation	Stability in Water	Transport & Distribution	Biodeg-radation	Acute Toxicity to Fish	Acute Toxicity to Inverte-brates	Acute Tox. to Aquatic Plants	Chronic Tox. to Aquatic Invertebrates
Subcategory II – Fatty Acid Reaction Products with Amino Compounds								
68131-13-5	C	C	C	C	C	C	C	
8051-30-7	C	C	C	C	C	C	C	
61790-63-4	C	C	C	C	C	C	C	
61790-69-0	C	C	C	C	C	C	C	
68132-46-7	C	C	C	C	C	C	C	
68910-93-0	C	C	C	A	A	C	C	
64754-93-4	C	C	C	C	C	C	C	
68910-87-2	*C*	*C*	*C*	*C*	*C*	*C*	*C*	
68953-36-6	C	C	C	C	C	C	C	
71820-35-4	C	C	C	C	C	A	C	

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data.
A = Endpoint fulfilled by adequate reliable data or model data.
C = Endpoint fulfilled by category read-across from existing or proposed test data.

Table 2 (continued)

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Environmental Fate and Ecotoxicity

CAS RN	Photodeg-radation	Stability in Water	Transport & Distribution	Biodeg-radation	Acute Toxicity to Fish	Acute Toxicity to Inverte-brates	Acute Tox. to Aquatic Plants	Chronic Tox. to Aquatic Invertebrates
Subcategory III – Imidazole Derivatives								
68122-86-1	C	C	C	A	A	C	C	
61791-39-7	C	C	C	C	C	A	C	
68442-97-7	C	C	C	C	C	C	C	
72623-72-4	C	C	C	C	C	C	C	
72749-55-4	C	C	C	C	C	C	C	
65817-50-7	C	C	C	C	C	C	C	
Subcategory IV – FND Amphoterics								
693-33-4	A	NC	A	A	A	A	A	
4292-10-8	*C*	*C*	*C*	*A*	*C*	*C*	*A*	
61789-39-7	C	C	C	C	A	C	C	
61789-40-0	C	C	C	A	A	A	A	
70851-07-9	*C*	*C*	*C*	*A*	*C*	*C*	*C*	

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data.
A = Endpoint fulfilled by adequate reliable data or model data.
C = Endpoint fulfilled by category read-across from existing or proposed test data.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

Table 3

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Human Health-Related Data

CAS RN	Acute Oral Toxicity	Acute Inhalation Toxicity	Acute Dermal Toxicity	Repeated Dose Toxicity	Genetic Toxicity *In vitro*	Toxicity to Reproduction	Developmental Toxicity
Subcategory I: Substituted Amides							
142-78-9	C	C	C	C	A	C	C
120-40-1	A	C	A	A	A	A	A [b]
68155-06-6	*A*	*C*	*C*	*C*	*A*	*C*	*A* [c]
61790-31-6	*A*	*C*	*C*	*C*	*C*	*C*	*C*
124-26-5	A	C	C	C	A	C	C
110-30-5	C	A	C	C	A	C	C
68140-00-1	A	C	A	A	A/OECD 473 [a]	A	C
68603-42-9	A	C	A	C	C	C	A
68140-01-2	C	C	C	C	C	C	C
301-02-0	A	C	C	C	A	C	C
93-83-4	C	C	C	C	C	C	C
68155-20-4	C	A	C	C	C	C	C
68425-47-8	C	C	C	C	C	C	C
112-84-5	A	C	C	A	A	C	C

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data or proposed testing.
A = Endpoint fulfilled by adequate reliable data.
OECD = Specified test guideline for proposed study.
C = Endpoint fulfilled by category read-across from existing or proposed test data.

[a] Data are lacking for mammalian cytogenetics, although bacterial cell mutation data are available.
[b] Data for CAS RN 68603-42-9 are also appropriate since CAS RN 120-40-1 is a major component (44 – 53%).
[c] CAS RNs 68155-06-6 (C12 - C18) and 68603-42-9 (C8 - 16) are very similar and the developmental toxicity study is considered to represent both compounds.

Table 3 (continued)

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Human Health-Related Data

CAS RN	Acute Oral Toxicity	Acute Inhalation Toxicity	Acute Dermal Toxicity	Repeated Dose Toxicity	Genetic Toxicity *In vitro*	Toxicity to Reproduction	Developmental Toxicity
Subcategory II – Fatty Acid Reaction Products with Amino Compounds							
68131-13-5	C	C	C	C	C	C	C
8051-30-7	C	C	C	C	C	C	C
61790-63-4	C	C	C	C	C	C	C
61790-69-0	C	C	C	C	C	C	C
68132-46-7	C	C	C	C	C	C	C
68910-93-0	C	C	C	C	C	C	C
64754-93-4	C	C	C	C	C	C	C
68910-87-2	*C*	*C*	*C*	*C*	*A*	*C*	*C*
68953-36-6	C	C	C	C	C	C	C
71820-35-4	A	C	C	C	A/OECD 473 [a]	C	C
Subcategory III – Imidazole Derivatives							
68122-86-1	A			A	A	A	A
61791-39-7	C	C	C	C	C	C	C
68442-97-7	A	C	C	C	C	C	C
72623-72-4	C	C	C	C	C	C	C
72749-55-4	C	C	C	C	C	C	C
65817-50-7	C	C	C	C	C	C	C

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data or proposed testing.
A = Endpoint fulfilled by adequate reliable data.
OECD = Specified test guideline for proposed study.
C = Endpoint fulfilled by category read-across from existing or proposed test data.
[a] Data are lacking for mammalian cytogenetics, although bacterial cell mutation data are available.

Table 3 (continued)

Proposed Test Plan for American Chemistry Council FND Amides Chemical Category
Human Health-Related Data

CAS RN	Acute Oral Toxicity	Acute Inhalation Toxicity	Acute Dermal Toxicity	Repeated Dose Toxicity	Genetic Toxicity *In vitro*	Toxicity to Reproduction	Developmental Toxicity
Subcategory IV – FND Amphoterics							
693-33-4	C	C	C	C	C	C	A
4292-10-8	*C*	*C*	*C*	*C*	*C*	*C*	*C*
61791-39-7	C	C	C	C	C	C	C
61789-39-7	C	C	C	C	C	C	C
61789-40-0	A	C	A	A	A/OECD 473 [a]	A	C
70851-07-9	*C*	*C*	*C*	*C*	*C*	*C*	*C*

Note: CAS RNs and data in italics are for supporting chemicals [non-HPV].
Shaded areas represent adequate reliable data, adequate model data or proposed testing.
A = Endpoint fulfilled by adequate reliable data.
OECD = Specified test guideline for proposed study.
C = Endpoint fulfilled by category read-across from existing or proposed test data.
[a] Data are lacking for mammalian cytogenetics, although bacterial cell mutation data are available.

Fatty Nitrogen Derived Amides High Production Volume (HPV) Chemicals Challenge

Assessment of Data Availability

Prepared for:

American Chemistry Council
Fatty Nitrogen Derivatives Panel
Amides Task Group

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Fatty Nitrogen Derived Amides
High Production Volume (HPV) Chemicals Challenge
Assessment of Data Availability

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Fatty Nitrogen Derived Amides
High Production Volume (HPV) Chemicals Challenge
Assessment of Data Availability

Introduction

Surfactants have a long history of safe use and have been studied extensively for environmental fate and human health effects. The chemicals in the Fatty Nitrogen Derived (FND) Amides Chemical Category of surfactants are similar to the class in general as to physical/chemical properties, environmental fate and toxicity. Some typical applications of FND Amides are: masonry cement additive; curing agent for epoxy resins; closed hydrocarbon systems in oil field production, refineries and chemical plants; and slip and antiblocking additives for polymers.

The safety of the FND Amides to humans is recognized by the U.S. FDA, which has approved stearamide, oleamide and/or erucamide for adhesives; coatings for articles in food contact; coatings for polyolefin films; defoaming agents for manufacture of paper and paperboard; animal glue (defoamer in food packaging); in EVA copolymers for food packaging; lubricants for manufacture of metallic food packaging; irradiation of prepared foods; release agents in manufacture of food packaging materials, food contact surface of paper and paperboard; cellophane in food packaging; closure sealing gaskets; and release agents in polymeric resins and petroleum wax. The low order of toxicity indicates that the use of FND Amides does not pose a significant hazard to human health.

Definition of Fatty Nitrogen Derived (FND) Amides Structure-Based Chemical Category and Subcategories

The FND Amides Chemical Category is comprised of 29 separate chemicals with unique CAS Registry Numbers (RNs). To facilitate the evaluation, interpretation and comparisons of available data for SIDS/HPV endpoints, the category was divided into the following four subcategories:

Subcategory I:	Substituted Amides
Subcategory II:	Fatty Acid Reaction Products with Amino Compounds (Note: Subcategory II chemicals, in many cases, contain Subcategory I chemicals as major components.)
Subcategory III:	Imidazole Derivatives
Subcategory IV:	FND Amphoterics

Subcategory I includes 12 substituted amides and Subcategory II includes 9 fatty acid amides reacted with amino compounds. Subcategory III represents five heterocyclic imidazole chemicals and Subcategory IV represents three amphoteric amides.

In addition, six non-HPV chemicals, which are structurally related to the category, were identified as supporting chemicals by the ACC FND Panel, Amides Task Group to provide additional data for the category (two chemicals in Subcategory I, one chemical in Subcategory II, one chemical in Subcategory III, and two chemicals in Subcategory IV). Information for these supporting chemicals is included in the table below and throughout the discussion.

Compositional Information for the FND Amides HPV and Supporting Chemicals

The FND Amides chemicals are identified in the following table:

Text Table A: CAS Registry Numbers and Chemical Names

CAS RN	Chemical Name
Subcategory I – Substituted Amides	
142-78-9	Dodecanamide, N-(2-hydroxyethyl)-
120-40-1	Dodecanamide, N,N-bis(2-hydroxyethyl)-
68155-06-6	*Amides, C12-18, N,N-bis(hydroxyethyl)*
61790-31-6	*Amides, tallow, hydrogenated*
124-26-5	Stearamide
110-30-5	Octadecanamide, N,N'-ethylenebis
68140-00-1	Amides, coco, N-(hydroxyethyl)
68603-42-9	Amides, coco, N,N-bis(hydroxyethyl)
68140-01-2	Amides, coco, N-[3-(dimethylamino)propyl]
301-02-0	Oleamide
93-83-4	Oleamide, N,N-bis(2-hydroxyethyl)-
68155-20-4	Amides, tall-oil fatty, N,N-bis(hydroxyethyl)
68425-47-8	Amides, soya, N,N-bis(hydroxyethyl)
112-84-5	Erucamide

Note: Chemicals in italics are supporting chemicals [non-HPV].

Text Table A: CAS Registry Numbers and Chemical Names (continued)

CAS RN	Chemical Name
Subcategory II – Fatty Acid Reaction Products with Amino Compounds	
68131-13-5	Naphthenic acids, reaction products with diethylenetriamine
8051-30-7	Coconut oil, reaction products with diethanolamine
61790-63-4	Fatty acids, coco, compounds with diethanolamine
61790-69-0	Fatty acids, tall-oil, reaction with diethylenetriamine
68132-46-7	Fatty acids, tall oil, compounds, with triethanolamine
68910-93-0	Fatty acids, tall-oil, reaction products with polyethylenepolyamines
64754-93-4	Fatty acids, tall-oil, reaction products with polyethylenepolyamines, acetates (essentially acetates of CAS RN 68910-93-0)
68910-87-2	*Fatty acids, tall-oil, reaction products with polyalkylenepolyamines, dodecylbenzenesulfonates*
68953-36-6	Fatty acids, tall-oil, reaction products with tetraethylenepentamine
71820-35-4	Fatty acids, tall-oil, low boiling, reaction products with 1-piperazineethanamine
Subcategory III – Imidazole Derivatives	
68122-86-1	*Imidazolium compounds, 4,5-dihydro-1-methyl-2-nortallow alkyl-1-(2-tallow amidoethyl) Me sulfate*
61791-39-7	1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-nortall-oil alkyl derivatives
68442-97-7	1H-Imidazole-1-ethanamine, 4,5-dihydro-, 2-nortall-oil alkyl derivatives
72623-72-4	Amides, C14-18, N-[2-(C13-17-alkyl-4,5-dihydro-1H-imidazol-1-yl)ethyl]
72749-55-4	Imidazolium cmpds., 2-(C17 & C17-unsatd. Alkyl)-1[2-(C18 & C18-unsatd. amido) ethyl]-4,5-dihydro-1-methyl, Me sulfates
65817-50-7	1,2-Ethanediamine, N-(2-aminoethyl)-N'-{2-(8Z)-8-heptadecenyl-4,5-dihydro-1H-imidazol-1-yl}ethyl

Note: Chemicals in italics are supporting chemicals [non-HPV].

Text Table A: CAS Registry Numbers and Chemical Names (continued)

CAS RN	Chemical Name
Subcategory IV – FND Amphoterics	
693-33-4	Ammonium, (carboxymethyl)hexadecyldimethyl-, hydroxide, inner salt
4292-10-8	*1-Propanaminium, N-(carboxymethyl)-N,N-dimethyl-3-[(1-oxododecyl)amino]-, inner salt*
61789-39-7	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-dimethyl-, N-coco acyl derivatives, chlorides, sodium salts
61789-40-0	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivatives, inner salt
70851-07-9	*Amides, coco, N-[3-(dimethylamino)propyl], alkylation products with chloroacetic acid, sodium salts*

Note: Chemicals in italics are supporting chemicals [non-HPV].

Structural Information for the FND Amides HPV and Supporting Chemicals

The following table presents the molecular formula and molecular weight data for the chemicals in FND Amides Category with definable structures. The structures for these chemicals as well as those in the category with structures that can be graphically represented are provided in Table 1.

Text Table B: Molecular Formula and Molecular Weight of Chemicals with Defined Structures

CAS RN	Chemical Name	Molecular Formula	Molecular Weight
Subcategory I – Substituted Amides			
142-78-9	Dodecanamide, N-(2-hydroxyethyl)-	$C_{14}H_{29}NO_2$	243
120-40-1	Dodecanamide, N,N-bis(2-hydroxyethyl)-	$C_{16}H_{33}NO_3$	287
124-26-5	Stearamide	$C_{18}H_{37}NO$	283
110-30-5	Octadecanamide, N,N'-ethylenebis	$C_{38}H_{76}N_2O_2$	593
301-02-0	Oleamide	$C_{18}H_{35}NO$	281
93-83-4	Oleamide, N,N-bis(2-hydroxyethyl)-	$C_{22}H_{43}NO_3$	375
112-84-5	Erucamide	$C_{22}H_{43}NO$	337

Text Table B: Molecular Formula and Molecular Weight of Chemicals with Defined Structures (continued)

Subcategory III – Imidazole Derivatives			
Subcategory IV – FND Amphoterics			
693-33-4	Ammonium, (carboxymethyl)hexadecyldimethyl-, hydroxide, inner salt	$C_{20}H_{41}NO_2$	327
4292-10-8	*1-Propanaminium, N-(carboxymethyl)-N,N-dimethyl-3-[(1-oxododecyl)amino]-, inner salt*	*$C_{19}H_{38}N_2O_3$*	*342*

Rationale for the FND Amides Structure-Based Chemical Category

The FND Amides surfactants are included as a single HPV chemical category based on the following generalities:

- Structural and functional similarities;
- Similar measured and modeled physical properties;
- Biodegradability;
- Aquatic toxicity observed at low concentrations, as observed with surfactants in general;
- Minimal or negligible mammalian toxicity; and
- Similar use and disposition patterns.

Available Data to Fulfill HPV Screening Information Data Set (SIDS) Endpoints

Approach to Evaluate the Database for the FND Amides Chemical Category

The following approach was used to obtain and analyze data relevant to the assessment of the FND Amides Chemical Category.

1. The chemical names and CAS RNs of the 29 HPV FND Amides chemicals supported by the ACC FND Panel, Amides Task Group (Task Group) were provided.
2. The names of six non-HPV supporting chemicals and their CAS registry numbers, considered similar to the members of the proposed FND Amides Chemical Category, were also provided by the Task Group.
3. Available published and unpublished reports were obtained from the members of the Task Group; they were organized and reviewed to identify studies that could fulfill SIDS endpoints.

4. Pertinent databases[1] were searched and all relevant reports were obtained to establish the full extent and nature of the published literature for the 29 FND Amides HPV and six supporting chemicals.
5. Each of the reports obtained was reviewed to determine adequacy according to EPA criteria and reliability according to Klimisch *et al.* (1997).
6. Robust summaries were prepared for each report with Klimisch score of 1 or 2, according to the guidelines proposed by the EPA (U. S. EPA, 1999a) for each study type.
7. When possible, estimates for physical/chemical properties, environmental fate and ecotoxicity values were developed by using appropriate Quantitative Structure Activity Relationships (QSARs).
8. When possible, fugacity modeling (Level 3) was performed to estimate transport and distribution into environmental compartments.

Use of Structure Activity Relationships for the FND Amides Chemical Category

Approaches recommended in the EPA document on the use of structure activity relationship (SAR) in the HPV Chemicals Challenge Program were employed in the assessment of the FND Amides Category (U. S. EPA, 1999b). Several models were employed to support the review and assessment of the FND Amides Category chemicals. The models included several based on structure-activity relationships (SAR), as well as Mackay-type fugacity-based modeling. The SAR models for physical properties were used to estimate boiling points, melting points, aqueous solubilities, octanol-water partition coefficients and vapor pressures. Other SAR models were used to estimate hydroxyl radical mediated atmospheric photo-oxidation and biodegradation potential. SAR models also were used to obtain conservative estimates of acute toxicity to aquatic organisms.

Common Features of the Models

All of the models (except the Mackay-type models) require the input of a molecular structure to perform the calculations. The structure must be entered into the model in the form of a Simplified Molecular Input Line Entry System (SMILES) notation or string. SMILES is a chemical notation system used to represent a molecular structure by a linear string of symbols. The SMILES string allows the program to identify the presence or absence of structural features used by the submodels to determine the specific endpoint. The models contain files of structures and SMILES strings for approximately 100,000 compounds, accessible via CAS RNs. SMILES strings cannot be developed for mixtures or chemicals without a single, definable structure.

[1] Databases include ChemIDplus HSDB (Hazardous Substances Data Bank), IRIS (Integrated Risk Information System), CCRIS (Chemical Carcinogenesis Research Information System), GENE-TOX, EMIC (Environmental Mutagen Information Center), DART/ETIC (Developmental and Reproductive Toxicology and Environmental Teratology Information Center), MEDLINE, TOXLINE, RTECS (Registry of Toxic Effects of Chemical Substances),TSCATS (Toxic Substances Control Act Test Submissions),IUCLID, 1996 (International Uniform Chemical Information Database)

Estimation of Physical/Chemical Properties
The SAR models for estimating physical properties and abiotic degradation were obtained from Syracuse Research Corporation 2000 (Estimation Programs Interface for Windows, Version 3.05 or EPIWIN v.3.05). The models were used to calculate melting point, boiling point, vapor pressure (submodel MPBPVP), octanol-water partition coefficient (K_{ow}) (submodel KOWWIN) and aqueous solubility (submodel WSKOWWIN). The calculation procedures are described in the program guidance and are adapted from standard procedures based on analysis of key structural features (Meylan and Howard, 1999a, b and c).

Estimation of Environmental Fate Properties
Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (Meylan and Howard, 2000a). The estimation methods employed by AOPWIN are based on the SAR methods developed by Dr. Roger Atkinson and co-workers (Meylan and Howard, 2000a). The SAR methods rely on structural features of the subject chemical. The model calculates a second-order rate constant with units of cm^3/molecules-sec. Photodegradation based on atmospheric photo-oxidation is in turn based on the rate of reaction (cm^3/molecules-sec) with hydroxyl radicals (HO•), assuming first-order kinetics and an HO• concentration of 1.5 E + 6 molecules/cm^3 and 12 hours of daylight. Pseudo first-order half-lives ($t_{1/2}$) were then calculated as follows: $t_{1/2} = 0.693/[(k_{phot} \times HO\bullet) \times (12\text{-hr}/24\text{-hr})]$.

Biodegradation potential was estimated using the submodel BIOWIN (Meylan and Howard, 2000b). BIOWIN estimates the probability for the rapid aerobic biodegradation of an organic chemical in the presence of mixed populations of environmental micro-organisms. Estimates are based on fragment constants that were developed using multiple linear and nonlinear regression analyses (Meylan and Howard, 2000b). BIOWIN uses the probabilities to estimate a potential pseudo first-order half-life for aerobic biodegradation of the subject chemical in surface water, soil and sediment.

Estimation of Environmental Distribution
The Level 3 Mackay-type fugacity-based models were obtained from the Trent University's Modeling Center. The specific model used was the generic Equilibrium Concentration model (EQC) Level 3, version 1.01. These models are described in Mackay *et al*. (1996a and b). Fugacity-based modeling is based on the "escaping" tendencies of chemicals from one phase to another. For instance, a Henry's Law constant calculated from aqueous solubility and vapor pressure is used to describe the "escape" of a chemical from water to air or vice versa, as equilibrium between the phases is attained. The key physical properties required as input parameters into the model are melting point, vapor pressure, K_{ow} and aqueous solubility. The model also requires estimates of first-order half-lives in the air, water, soil and sediment. An additional key input parameter is loading of the chemical into the environment.

Estimation of Acute Aquatic Toxicity
Models developed by the U. S. Environmental Protection Agency (EPA) were employed to make estimates of acute toxicity to aquatic organisms, specifically to the fathead minnow (*Pimephales promelas*), a commonly tested fish; a water-column dwelling invertebrate (*Daphnia magna*); and to a commonly tested green alga, *Selenastrum capricornutum*. The models are incorporated in a modeling package called ECOSAR, version 0.99f (U. S. EPA, 2000). ECOSAR may be obtained from the EPA website for the Office of Pollution Prevention and Toxics, Risk

Assessment Division. The models calculate inherent toxicity based on structural features and physical properties, mainly the K_{ow} (Meylan and Howard, 1998).

Modeling Information Specific to the FND Amides Category

When CAS RNs were included in the files of structures, the models described above were used for the FND Amides Category chemicals and the six non-HPV supporting chemicals. Estimations of physical properties, environmental fate and distribution, and ecotoxicity were not possible for 20 of the 29 HPV chemicals in the FND Amides Category because they do not have single definable structures and/or were not available in the files of structures of the models. Model predictions were available for one of the six non-HPV supporting chemicals. The model did not provide estimates of stability in water for this class of chemicals because the model cannot calculate this parameter for chemicals that do not meet the criteria of neutral organic compounds with structures that can be hydrolyzed. Since the FND Amides Category chemicals are considered to be released into wastewater treatment systems for treatment prior to release into surface water, release to soil and air were considered to be minor avenues of entry for FND Amides Category chemicals into the environment. Therefore, for fugacity modeling, all input was assumed to be into surface water using the chemical-specific parameters to attain estimates of the chemical distributions between environmental compartments.

Availability of Reliable Data for the FND Amides Chemical Category

Robust summaries for SIDS/HPV endpoint studies and other supporting studies with reliable data (according to Klimisch criteria) for the HPV and supporting chemicals are provided in Appendix A and are summarized in Tables 2 through 4.

In Subcategory I, reliable data were available for three chemicals for melting point, one chemical for boiling point, and three chemicals for water solubility to meet the physical/chemical properties SIDS/HPV endpoints.

Reliable data were available for biodegradation and aquatic toxicity endpoints as shown in the following table:

Text Table C: Number of Available Reliable Environmental Fate and Ecotoxicity Studies

Subcategory	Biodegradation	Acute/Prolonged Toxicity to Fish	Acute Toxicity to Invertebrates	Acute Tox. to Aquatic Plants	Chronic Tox. to Aquatic Invertebrates
I	9 (6)	4 (4)	3 (2)	1(1)	1 (1)
II	1 (1)	1 (1)	1 (1)	--	--
III	1 (1)	1 (1)	1 (1)	--	--
IV	9 (3)	5 (2)	5 (2)	5 (2)	--

Note: The number in parentheses indicates the number of chemicals with reliable data
-- No reliable data are available

Reliable data were available for human health-related toxicity endpoints as shown in the following table:

Text Table D: Number of Available Reliable Human Health-Related Studies

Subcategory	Acute Oral Tox.	Acute Inhalation Tox.	Acute Dermal Tox.	Repeated Dose Tox.	Genetic Tox.	Developmental Tox.
I	14 (8)	2 (2)	3 (3)	3* (3)	8 (8)	1 (1)
II	2 (1)	--	--	--	3 (2)	--
III	3 (2)	--	--	2* (1)	3 (1)	2 (1)
IV	4 (1)	--	1 (1)	3* (1)	5 (1)	1 (1)

Note: The number in parentheses indicates the number of chemicals with reliable data
-- No reliable data are available
* At least one study meets the SIDS requirement for a reproductive screen (i.e. histological evaluation of reproductive organs)

Physical/Chemical Properties QSAR Estimates and Correlation to Reliable Data

The available reliable data and QSAR estimates for physical/chemical properties of the FND Amides chemicals are presented in Table 2. Robust summaries for the reliable studies are provided in Appendix A.

As described above, where data gaps existed in Table 2, the physical/chemical property estimation program EPIWIN version 3.05 was used to derive estimates. The EPIWIN estimates must be interpreted with a great deal of professional judgment.

The QSAR estimates are based on structure and, therefore, can be made only for substances for which a structure can be defined. Thus, a complete set of model data was generated only for the chemicals with discrete structures. These included seven HPV chemicals and one supporting chemical from Subcategory I and one HPV chemical from Subcategory IV. For modeling of the non-HPV supporting chemical in Subcategory I (CAS RN 68155-06-6), the structure of average chain length (C_{15}) was used. The HPV chemical from Subcategory II, CAS RN 68443-85-6, was not modeled since a SMILES structure was not available even though the chemical has a definable structure. The compositional variability of the chemicals without definable structures also makes the experimental measurement of physical/chemical properties of these chemicals of minimal practical value for prediction of their environmental behavior or toxicological properties. Therefore, the chemicals in the FND Amides Chemical Category without defined structures are best supported by the other chemicals in the category for which the properties can be measured and/or modeled.

The available data for physical/chemical properties are summarized below:

Subcategory I - Substituted Amides
EPIWIN predicted melting points ranged from 152 to 323 °C. When compared to measured values, the model estimates were 162, 152 and 159 °C for the three chemicals with measured melting points of approximately 39, 109 and 76 °C, respectively. Company literature for melting points was concordant with reliable data for CAS RNs 124-26-5 and 301-02-0 and provided a melting point of 80 °C for CAS RN 112-84-5 as compared to a predicted value of 183 °C.

Estimates made for boiling points ranged from 404 to 736 °C, compared with the single measured value of approximately 250 °C (model estimate for this chemical was 411 °C).

As expected, based on extensive practical experience with these and similar large organic molecules, the EPIWIN estimated vapor pressures were extremely low across the Subcategory, i.e. seven to 18 orders of magnitude lower than water. The FND Amides in this Subcategory are essentially nonvolatile, as is generally the case for molecules of this size and complexity.

Predicted or measured K_{ow} values are of limited practical use for the FND Amides Category chemicals. An inherent property of surfactants is that they accumulate at the interface between hydrophobic and hydrophilic phases rather than equilibrating between the two phases. Therefore, the accurate measurement of the K_{ow} of any surfactant is notoriously difficult. Even if such measurements were made accurately, the K_{ow} is not an appropriate value by which to predict the partitioning behavior of the FND Category Amides in the environment because of the tendency of surfactants to partition at lipid/aqueous interfaces. The EPIWIN estimated values for the octanol/water partition coefficient (log K_{ow}) ranged from 2.39 to approximately 14. Since model estimates for the log K_{ow} for the two chemicals (CAS RNs 142-78-9 and 120-40-1) and the supporting non-HPV chemical (CAS RN 68155-06-6) were much lower in comparison to the other members of Subcategory I, it is likely that these predicted values are low and, subsequently, the predicted water solubility values for these chemicals are overestimates.

Model predictions for water solubility ranged from virtually insoluble (<< 0.1 mg/l) to slightly soluble (approximately 158 mg/l). However, the two modeled values (CAS RNs 142-78-9 and 68155-06-6) above 1 mg/l are suspect since measured values for three of the chemicals in the Subcategory indicate these chemicals as well as the other modeled values are "insoluble."

Subcategory II – Fatty Acid Reaction Products with Amino Compounds
No model estimates were available for the chemicals in Subcategory II. In addition, no reliable data were available for melting point, boiling point, vapor pressure, or partition coefficient. Company literature for seven of the 14 chemicals in the subcategory indicated that the chemicals were insoluble in water.

Subcategory III - Imidazole Derivatives
No model estimates were available for the chemicals in Subcategory III. Available company literature indicated that CAS RN 61791-39-7 is dispersible and CAS RN 68442-77-3 is insoluble in water.

Subcategory IV - FND Amphoterics
The chemical in this FND Amphoterics Subcategory with a definable structure (CAS RN 693-33-4) was predicted to be similar to other chemicals in the FND Amides Category for melting point (243 °C), boiling point (566 °C) and non-volatility. As with chemicals in Subcategories I, the predicted log K_{ow} was lower than expected and thus, the predicted water solubility was higher than expected (171 mg/l).

Summary - Physical/Chemical Properties
For melting and boiling points, model estimates were within a factor of two to four times the measured values. Vapor pressures were estimated to be very low, as expected, and the FND

Amides were considered to be essentially nonvolatile. The available water solubility measurements indicated the chemicals are insoluble in water and available company literature supported the measurements, but model estimates varied from insoluble to slightly soluble. Log K_{ow} values less than 5 were obtained for some chemicals, which presumably resulted in the estimates of the higher than expected water solubility in those cases. It is important to note that predicted or measured K_{ow} values are of limited practical use for the FND Amides Category chemicals because, like other surfactants, they tend to accumulate at the interface between hydrophobic and hydrophilic phases rather than equilibrating between the two phases. Therefore, the accurate measurement of the K_{ow} of a surfactant is notoriously difficult. Even if such measurements were made accurately, the K_{ow} is not an appropriate value by which to predict the partitioning behavior of the FND Amides Category chemicals in the environment because of the tendency of surfactants to partition at lipid/aqueous interfaces. Overall, the available data support the conclusion that, because of their closely-related structures, FND Amides possess similar physical/chemical properties across the category.

Environmental Fate and Ecotoxicity QSAR Estimates and Correlation to Reliable Data

The available reliable data and QSAR estimates for the environmental fate and effects of the FND Amides chemicals are presented in Table 3. Robust summaries for the reliable studies are provided in Appendix A.

Subcategory I - Substituted Amides
Models for atmospheric photodegradation were used according to EPA guidelines. However, the fugacity models predict virtually no occurrence of the HPV substances in air. Nonetheless, modeling of the HPV substances in Subcategory I indicates that these chemicals would be expected to degrade relatively rapidly upon exposure to light ($t_{1/2}$ values ranging from approximately 2 to 10 hours).

The model did not provide estimates of stability in water for this class of chemicals because the model cannot calculate this parameter for chemicals that do not meet the criteria of neutral organic compounds with structures that can be hydrolyzed. Due to the low water solubility of the chemicals in the FND Amides Chemical Category, water hydrolysis is of little practical significance.

Estimations of the transport and distribution in environmental media (percent in air, water, soil and sediment) following entry into the environment via water for the HPV chemicals and one supporting, non-HPV chemical that could be modeled are presented in Table 3. Of the eight modeled chemicals in Subcategory I, the distribution predictions for three chemicals were extensively to water (≥ 98% for CAS RNs 142-78-9, 120-40-1, and 68155-06-6), prediction for four chemicals was extensively to sediment (> 85% for CAS RNs 124-26-5, 110-30-5, 301-02-0, and 112-84-5) and the prediction for one of the chemicals (CAS RN 93-83-4) was 34% and 66% in water and sediment, respectively. In all cases, air and soil did not represent significant reservoirs in the fugacity model.

For biodegradation, measured data exist for five of the 12 HPV chemicals and one non-HPV chemical in this Subcategory, indicating that these chemicals are biodegradable with degradation varying from readily degradable (CAS RNs 120-40-1, 61790-31-6, 68140-00-1 and 301-02-0) to

slowly degraded (CAS RN 112-84-5). Model predictions for biodegradation were made for the chemicals that could be modeled in the Subcategory and supported the conclusion that the Subcategory I chemicals are expected to biodegrade.

ECOSAR estimates for acute fish and daphnid toxicity as well as toxicity to algae were made. For fish and daphnid estimates, the model predicted that chemicals with very low water solubility are "not toxic at solubility" (Table 3)[2]. Also, estimates of LC_{50} values for those chemicals with predicted higher water solubility are presented in Table 3 (range of 12 to 87 mg/l). Measured acute fish toxicity data were available (LC_{50} values between 2.6 mg/l and 31 mg/l). In the case where a modeled value could be compared to measured values (CAS RN 93-83-4), the model prediction indicated "not toxic at solubility" (measured LC_{50} value was 2.6 mg/l), which suggests that the chemical may have been tested at concentrations that exceeded solubility (i.e. dispersions) or the model underestimated toxicity. In addition to the acute toxicity determinations, one chemical (CAS RN 112-84-5) was tested in a 28-day study with a NOEC determined to be > 0.105 mg/l. Measured values for toxicity to aquatic invertebrates were available for two of the HPV chemicals (CAS RNs 68140-00-1 and 68603-42-9). Similar to the data for fish, these EC_{50} data (approximately 2.5 and 38 mg/l) indicated greater toxicity than the models predicted. The model predicted values for algae toxicity were extremely variable (0.0004 mg/l to 61 mg/l) although such differences would not be expected based on molecular weight and functional groups in this Subcategory. A study evaluating the toxicity to aquatic plants was available for CAS RN 68140-00-1 in this Subcategory. The E_bC_{50} (EC_{50} for growth) was 1.1 mg/l. A study evaluating chronic toxicity to daphnid (CAS RN 112-84-5) indicated no toxicity at the two concentrations tested (highest analytical concentration was approximately 0.08 mg/l) and the no observable effect concentration (NOEC) was, therefore, 0.08 mg/l.

Subcategory II – Fatty Acid Reaction Products with Amino Compounds
No model data were available for this Subcategory. A single biodegradation study (CAS RN 68910-93-0) indicated biodegradation (approximately 35% in 126 days). Acute toxicity to fish for the same chemical indicated aquatic toxicity similar to other chemicals in the FND Amides Chemical Category (LC_{50} = 0.43 mg/l) as did a test in daphnid for CAS RN 71820-35-4 (EC_{50} = 0.3 mg/l).

Subcategory III - Imidazole Derivatives
No model data were available for this Subcategory. A measured value for biodegradation for the supporting, non-HPV chemical (CAS RN 68122-86-1) indicated slow biodegradation of 5% in 20 days. A fish toxicity study for the non-HPV chemical (CAS RN 68122-86-1) gave an LC_{50} value of 59 mg/l and a daphnid study for one of the HPV chemicals in the subcategory (CAS RN 61791-39-7) gave an EC_{50} of 1.5 mg/l, which were similar to the other chemicals in the FND Amides Chemical Category.

[2] Note that, in these cases, the model provides an estimated LC_{50} or EC_{50} value but states "chemical may not be soluble enough to measure this predicted effect." The preferred designation of "not toxic at solubility" is used since incorporation of the predicted value that is above the solubility or the use of the caveat as stated in the model provides for greater uncertainty.

Subcategory IV - FND Amphoterics

Modeled data for the FND Amphoteric chemical with defined structure (CAS RN 693-33-4) were similar to those for the other chemicals in the FND Amides Chemical Category. The model predicted rapid atmospheric photodegradation ($t_{1/2}$ = 6.4 hours), extensive distribution to the water compartment (> 99%) and rapid biodegradation ($t_{1/2}$ = 15 days). Aquatic toxicity estimates seem to be conservative, indicating the chemical to be toxic to fish (LC_{50} = 0.15 mg/l), invertebrates (EC_{50} = 0.15 mg/l) and algae (EC_{50} << 0.1 mg/l). The measured toxicity to daphnid (LC_{50} = 2.5 mg/l) was similar to other chemicals in the FND Amides Category and was almost 20-times less toxic than the model estimate. Substantial measured data for CAS RN 61789-40-0 were available for biodegradation, indicating the chemical was readily biodegradable in most assays, as well as for acute toxicity to fish (LC_{50} = 2.0 to approximately 7 mg/l) and daphnid (EC_{50} = 6.5 to 21.5 mg/l), and toxicity to algae (EC_{50} values from 0.55 to 48 mg/l). One algae study (CAS RN 4292-10-8) indicated a NOEC of 100 mg/l. A biodegradation study for the non-HPV chemical, CAS RN 70851-07-9, indicated the chemical was readily biodegradable (> 90% in 13 days).

Summary – Environmental Fate and Ecotoxicity

As anticipated in the EPA guidance for HPV chemicals, only model estimates were available for photodegradation and fugacity. The other exclusively modeled value, stability in water, could not be calculated for this group of chemicals. Atmospheric photodegradation was predicted to be rapid although fugacity models suggested virtually no distribution of these chemicals to the air. Predicted distribution of the chemicals in the environment was to water, sediment or both compartments based on the assumption that release of the chemicals to the environment is all via water. For chemicals with higher predicted water solubility (lower K_{ow}), the water compartment was favored. Measured and modeled biodegradation rates were in close agreement and indicated the FND Amides are biodegradable. Measured aquatic toxicity values indicated LC_{50} and EC_{50} values < 100 mg/l for fish, daphnid and algae except for a single algae study that had a NOEC at the only concentration used, 100 mg/l. The modeling programs were inconsistent in their predictability for aquatic toxicity endpoints, with some values similar to measured or expected and others divergent. The inaccurate/inappropriate prediction of the log K_{ow} (as described above) and, therefore, water solubility was considered the likely cause of these inconsistencies. Overall, the available data support the conclusion that, because of their closely-related structures, FND Amides possess similar environmental fate and ecotoxicity across the Category.

Human Health-Related Reliable Data

The human health effects data for SIDS endpoints of the 29 FND Amides chemicals and five related supporting chemicals are presented in Table 4. Robust summaries for the reliable studies are provided in Appendix A.

Subcategory I - Substituted Amides

Acute rat oral toxicity LD_{50} data were available for eight of the 14 chemicals in Subcategory I. Rat oral LD_{50}s are ≥ 3.5 g/kg indicating that the chemicals possess slight to negligible acute toxicity by the oral route. Rabbit acute dermal toxicity studies for three members of the Subcategory (CAS RNs 120-40-1, 68140-00-1 and 68603-42-9) confirmed the expected result that these chemicals have minimal acute toxicity in rabbits via skin application (no deaths at 2 g/kg). In addition, one acute inhalation study (CAS RN 110-30-5) indicted these chemicals

would be expected to have minimal acute inhalation toxicity (no deaths and minimal toxicity at 112 mg/m^3). An acute inhalation study to determine sensory irritation was also available (CAS RN 68155-20-4). Although not conducted to determine an LC_{50}, the study resulted in no toxicity at concentrations as high as 219 mg/m^3 with sensory irritation observed.

Repeated dose toxicity studies were available for three (CAS RNs 120-40-1, 68140-00-1 and 112-84-5) of the 14 chemicals in this Subcategory. The reported no observed adverse effect level (NOAEL) for CAS RN 112-84-5 was 7500 mg/kg/day (animals dosed via gavage with 10 doses each day for five days followed by a 23 day observation period); however, histopathological evaluation was not conducted so it is likely that in a longer-term study with detailed evaluations, the NOAEL would be less than 7500 mg/kg/day. For the more definitive 90-day feeding studies (CAS RNs 120-40-1 and 68140-00-1), the NOAELs were determined to be 50 and > 750 mg/kg/day, respectively. These 90-day studies indicated no organ specific or overt toxicity. For CAS RN 120-40-1, effects of general weight loss and other nonspecific responses were observed at the higher doses.

In vitro genetic toxicity studies (*Salmonella* reverse mutation assay) for eight of the 14 chemicals in this Subcategory indicated the chemicals are not mutagenic in this assay, as would be expected based on the structures and molecular weights.

Evaluation of potential reproductive effects in the HPV and SIDS processes are satisfied by the histological evaluation of reproductive organs in the 90-day repeat-dose toxicity studies for CAS RNs 120-40-1 and 68140-00-1. No effects on the gonads or other reproductive organs were observed at any dose level in these studies. Thus the NOAELs for reproductive screening were > 1000 and 750 mg/kg/day, respectively, which were the highest doses tested.

Developmental toxicity studies were conducted for one chemical in the Subcategory (CAS RN 68603-42-9). No effects were observed and thus the rat maternal and developmental NOAELs were greater than the highest dose tested of 1000 mg/kg/day. The chemical with CAS RN 68155-06-6 is very similar to CAS RN 68603-42-9 (C12 – C18 vs. C8 – C16, respectively) and the testing for CAS RN 68603-42-9 is considered appropriate for both materials. In addition, CAS RN 120-40-1 is a major component of these chemicals (44 – 53%), thus its developmental toxicity potential is adequately addressed as well.

Subcategory II – Fatty Acid Reaction Products with Amino Compounds
Two acute oral toxicity studies for one chemical (CAS RN 71820-35-4) were available. They indicated slight oral toxicity with the lowest determined LD_{50} equal to approximately 3.6 g/kg.

In vitro mutagenicity tests (*Salmonella* reverse mutation assay) were available for two chemicals (CAS RNs 68910-87-2 and 71820-35-4) in Subcategory II and indicated no mutagenic activity.

Subcategory III - Imidazole Derivatives
Acute oral toxicity studies for the non-HPV chemical, CAS RN 68122-86-1, indicated a low order of toxicity with LD_{50} values > 5 g/kg. An acute oral study for CAS RN 68442-97-7 was conducted at a single dose of 5 g/kg. Although no LD_{50} was defined, the mortality observed at 5 g/kg (60%) approximated the LD_{50}.

Two repeated dose toxicity studies were available for the non-HPV chemical, CAS RN 68122-86-1. In a 13-week dietary study in dogs, the only effects noted were slightly altered hematology measurements at the high dose of 40,000 ppm (approximately 1300 and 1950 mg/kg/day for males and females, respectively) and decreased cholesterol in males from the mid-dose group (12,000 ppm; 366 mg/kg/day) and males and females from the high-dose group. The NOAEL was considered to be the low dose of 4000 ppm (approximately 143 mg/kg/day for both sexes). In an older 91-day rat study (ca. 1957), the NOAEL was greater than 2200 mg/kg/day.

In vitro mutagenicity tests, including *Salmonella* reverse mutation, CHO cytogenetics, and Unscheduled DNA synthesis assays, were available for CAS RN 68122-86-1 and indicated no mutagenic or clastogenic activity.

Evaluation of potential reproductive effects in the HPV and SIDS processes are satisfied by the histological evaluation of reproductive organs in the 13-week repeat dose toxicity study for CAS RN 68122-86-1. No effects on the gonads or other reproductive organs were observed at any dose level in this study. Thus the NOAEL for reproductive screening was > 1322 mg/kg/day, the highest dose tested.

Developmental toxicity studies were conducted for CAS RN 68122-86-1. No effects were observed and thus the rat maternal and developmental NOAELs were greater than the highest dose tested of 1000 mg/kg/day. In addition, a probe study conducted to help set doses for the definitive developmental toxicity study, indicated no maternal or fetal toxicity up to the highest dose of 1875 mg/kg/day.

Subcategory IV - FND Amphoterics

Five acute toxicity studies were available for one chemical in Subcategory IV (CAS RN 61789-40-0). They indicated slight oral toxicity with the lowest determined LD_{50} greater than or equal to approximately 1.5 g/kg. An acute dermal study in rats indicate an LD_{50} value greater than 2 g/kg.

Three repeated dose toxicity tests were available CAS RN 61789-40-0. The NOAELs were 250 mg/kg/day and 500 mg/kg/day in a 90-day and a 28-day subchronic study, respectively. Gastric irritation was the primary finding in these studies. In addition, a LOAEL of 300 mg/kg/day based primarily on clinical signs was determined in a 7-day gavage study.

In vitro mutagenicity assays (*Salmonella* reverse mutation assay) were available for CAS RN 61789-40-0 and indicated no mutagenic activity. In addition, an *in vivo* mouse micronucleus assay was negative for this chemical.

Toxicity to reproduction was satisfactorily screened in the two repeated dose toxicity studies by histological evaluation of the reproductive organs. No effects were observed at any dose in either study and the NOAEL for reproductive screening for each study was > 1000 mg/kg/day.

A developmental toxicity study was conducted for CAS RN 693-33-4. The NOAEL was established as 50 mg/kg/day for maternal toxicity and 150 mg/kg/day for developmental toxicity. Effects in the fetuses at the highest dose of 250 mg/kg/day were considered biologically significant but related to maternal toxicity.

Summary – Human Health-Related Data

Adequate acute oral LD_{50} studies were available throughout the subcategories. They confirmed the slight acute toxicity of the chemical class with LD_{50} values greater than 1 g/kg. Repeated dose toxicity studies supported the conclusion that the chemicals in the FND Amides Chemical Category have minimal toxicity potential. Mutation assays for the HPV and supporting chemicals indicated a lack of mutagenic activity for the chemicals in the FND Amides Chemical Category. Reproductive screening from repeat dose toxicity studies and results from available developmental toxicity studies indicated that the FND Amides tested are unlikely to result in reproductive effects and are not developmental toxicants. Only minimal fetal effects were observed at maternally toxic doses in one developmental toxicity study. The available data support the conclusion that, because of their closely-related structures, the FND Amide chemicals possess similar human health-related data across the Category.

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Mackay, D., A. Di Guardo, S. Paterson, G. Kicsi and C. E. Cowan. 1996a. Assessing the Fate of New and Existing Chemicals: A Five-stage Process. *Environ. Toxicol. Chem*. 15(9):1618 - 1626.

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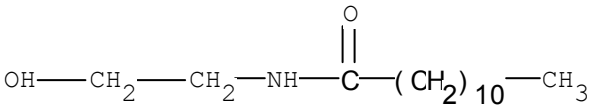
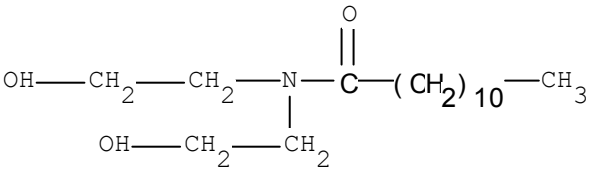
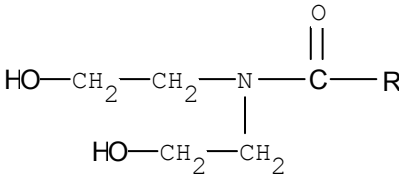
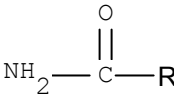
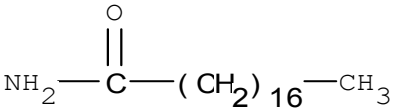
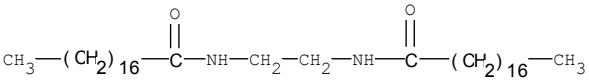
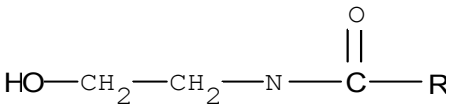
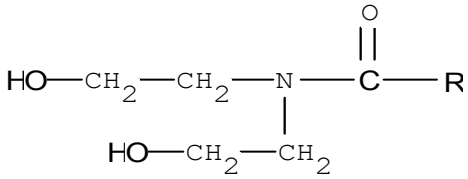
Table 1

Definable Structures of FND Amides Category Chemicals

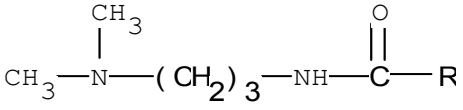
Subcategory I – Substituted Amides	
 Dodecanamide, N-(2-hydroxyethyl)- 142-78-9	 Dodecanamide, N,N-bis(2-hydroxyethyl)- 120-40-1
 **R = C_{12} – C_{18} alkyl[1]** *Amides, C12-18, N,N-bis(hydroxyethyl)* *68155-06-6*	 **R = tallow alkyl, hydrogenated[1]** *Amides, tallow, hydrogenated* *61790-31-6*
 Stearamide 124-26-5	 Octadecanamide, N,N'-ethylenebis 110-30-5
 **R = coco alkyl[1]** Amides, coco, N-(hydroxyethyl) 68140-00-1	 **R = coco alkyl[1]** Amides, coco, N,N-bis(hydroxyethyl) 68603-42-9

[1]Note: The total carbon number in the R group includes the C in the C=O bond shown.
Chemical names in italics are supporting chemicals [non-HPV].

Table 1 (continued)

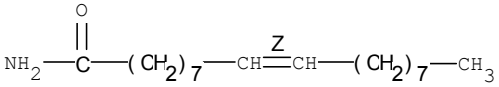
Definable Structures of FND Amides Category Chemicals (continued)

Subcategory I – Substituted Amides (continued)

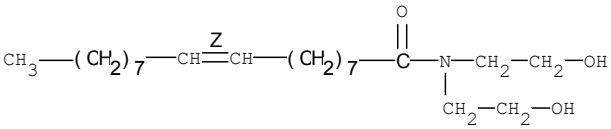


R = coco alkyl[1]

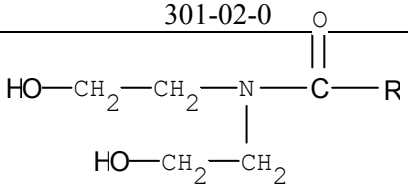
Amides, coco, N-[3-(dimethylamino)propyl]
68140-01-2



Oleamide
301-02-0

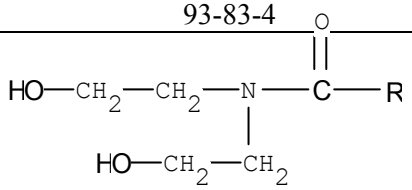


Oleamide, N,N-bis(2-hydroxyethyl)-
93-83-4



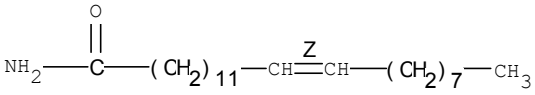
R = tall-oil fatty[1]

Amides, tall-oil fatty, N,N-bis(hydroxyethyl)
68155-20-4



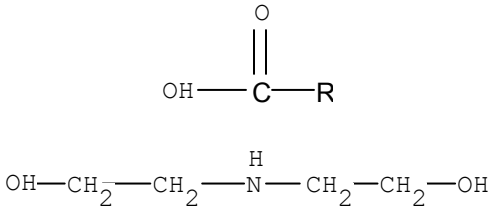
R = soya alkyl[1]

Amides, soya, N,N-bis(hydroxyethyl)
68425-47-8



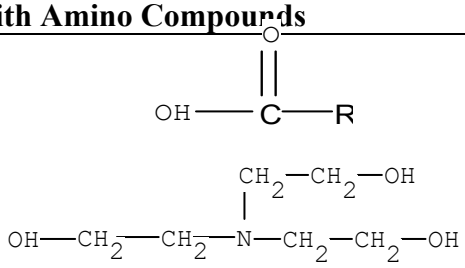
Erucamide
112-84-5

Subcategory II – Fatty Acid Reaction Products with Amino Compounds



R = coco alkyl[1]

Fatty acids, coco, compounds with diethanolamine
61790-63-4



R = tall oil alkyl[1]

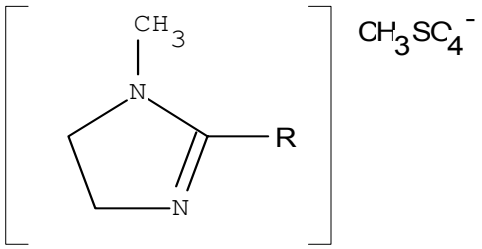
Fatty acids, tall oil, compounds, with
triethanolamine
68132-46-7

[1]Note: The total carbon number in the R group includes the C in the C=O bond shown.

Table 1 (continued)

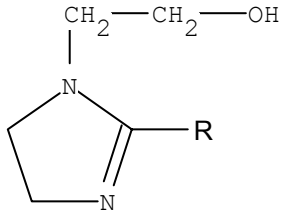
Definable Structures of FND Amides Category Chemicals (continued)

Subcategory III – Imidazole Derivatives



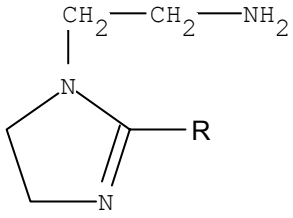
R = nortallow alkyl-1-(2-tallow amidoethyl)

Imidazolium compounds, 4,5-dihydro-1-methyl-2-nortallow alkyl-1-(2-tallow amidoethyl) Me sulfate
68122-86-1



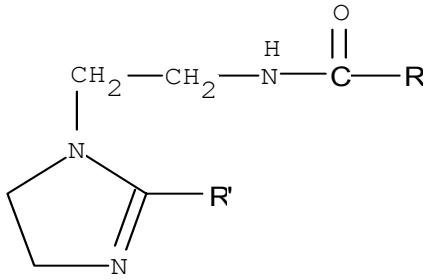
R = nortall-oil alkyl

1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-nortall-oil alkyl derivatives
61791-39-7



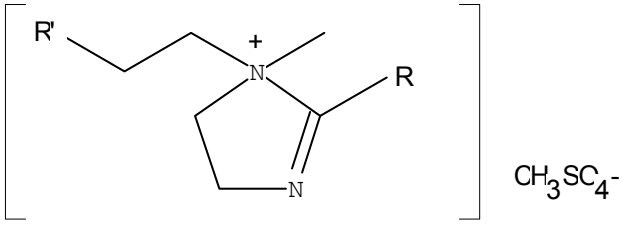
R = nortall-oil alkyl

1H-Imidazole-1-ethanamine, 4,5-dihydro-, 2-nortall-oil alkyl derivatives
68442-97-7



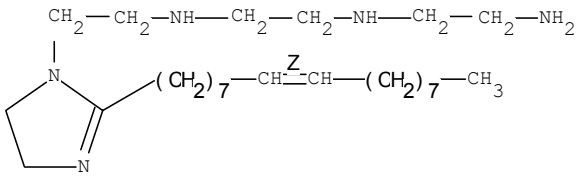
R = C_{14} – C_{18} alkyl
R' = C_{13} – C_{17} alkyl

Amides, C14-18, N-[2-(C13-17-alkyl-4,5-dihydro-1H-imidazol-1-yl)ethyl]
72623-72-4



R = C_{17} and C_{17}-unsatd. alkyl
R' = C_{18} and C_{18}-unsatd. amido

Imidazolium cmpds., 2-(C17 & C17-unsatd. Alkyl)-1[2-(C18 & C18-unsatd. Amido) ethyl]-4,5-dihydro-1-methyl, Me sulfates
72749-55-4



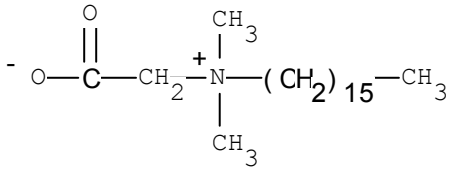
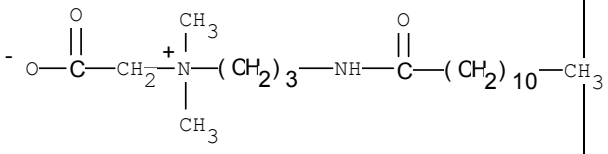
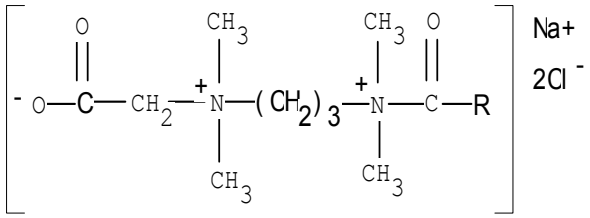
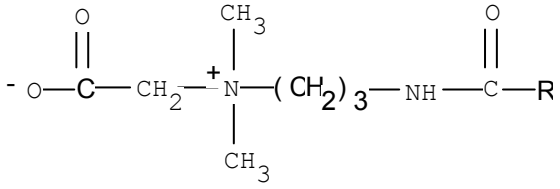
1,2-Ethanediamine, N-(2-aminoethyl)-N'-{2-(8Z)-8-heptadecenyl-4,5-dihydro-1H-imidazol-1-yl}ethyl
65817-50-7

Chemical names in italics are supporting chemicals [non-HPV].

Table 1 (continued)

Definable Structures of FND Amides Category Chemicals (continued)

Subcategory IV – FND Amphoterics

 Ammonium, (carboxymethyl)hexadecyl dimethyl-, hydroxide, inner salt 693-33-4	 *1-Propanaminium, N-(carboxymethyl)-N,N-dimethyl-3-[(1-oxododecyl)amino]-, inner salt* *4292-10-8*
 **R = coco alkyl[1]** 1-Propanaminium, 3-amino-N- (carboxymethyl)-N,N-dimethyl-, N-dimethyl-, N-coco acyl derivatives, chlorides, sodium salts 61789-39-7	 **R = coco alkyl[1]** 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivatives, inner salt 61789-40-0

[1]Note: The total carbon number in the R group includes the C in the C=O bond shown.
Chemical names in italics are supporting chemicals [non-HPV].

Table 2

Physical/Chemical Properties Data for FND Amides Chemical Category

CAS RN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility (mg/l)
Subcategory I: Substituted Amides					
142-78-9	154	404	6.6 E-9	3.24	43.9
120-40-1	**38.7** 162	431	6.7 E-9	2.89	**insoluble**
68155-06-6	*154*	*419*	*1 E-9*	*2.39*	*158*
61790-31-6					
124-26-5	**109** 152 99 [a]	**250 - 251** 411	6.7 E-7	6.70	**insoluble**
110-30-5	323	736	8 E-18	14	2 E-10
68140-00-1					
68603-42-9					
68140-01-2					
301-02-0	**76** 159 71 [a]	415	1.6 E-7	6.48	**insoluble**

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.

[a] Based on company literature.

Table 2 (continued)

Physical/Chemical Properties Data for FND Amides Chemical Category

CAS RN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility (mg/l)
Subcategory I: Substituted Amides (continued)					
93-83-4	204	504	5.9 E-13	5.62	0.07
68155-20-4					
68425-47-8					
112-84-5	183 80 [a]	461	8.3 E-8	8.44	0.0004
Subcategory II – Fatty Acid Reaction Products with Amino Compounds					
68131-13-5					Insoluble [a]
8051-30-7					
61790-63-4					
61790-69-0					Insoluble [a]
68132-46-7					Insoluble [a]
68910-93-0					Insoluble [a]
64754-93-4					Insoluble [a]
68910-87-2					
68953-36-6					Insoluble [a]
71820-35-4					

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.

[a] Based on company literature.

Table 2 (continued)

Physical/Chemical Properties Data for FND Amides Chemical Category

CAS RN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility (mg/l)
Subcategory III – Imidazole Derivatives					
68122-86-1					
61791-39-7					Dispersible [a]
68442-97-7					Insoluble [a]
72623-72-4					
72749-55-4					
65817-50-7					
Subcategory IV – FND Amphoterics					
693-33-4	243	566	2.4 E-12	2.44	171
4292-10-8					
61789-39-7					
61789-40-0					
70851-07-9					

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.

[a] Based on company literature.

Table 3

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution [a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory I: Substituted Amides								
142-78-9	k_{phot} = 31 E-12 $t_{1/2}$ = 8.3 hr	NC	air: < 1% water: 98% soil: < 1% sediment: 1%	$t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 60 d	12	14	10	
120-40-1	k_{phot} = 49 E-12 $t_{1/2}$ = 5.2 hr	NC	air: < 1% water: 99% soil: < 1% sediment: 1%	**79.7% $ThCO_2$ in 40 d** $t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 60 d	31	35	23	
68155-06-6	*k_{phot} = 48 E-12* *$t_{1/2}$ = 5.35 hr*	*NC*	*air: < 1%* *water: 99%* *soil: < 1%* *sediment: 0.5%*	*$t_{1/2}$ water = 15 d* *$t_{1/2}$ soil = 15 d* *$t_{1/2}$ sediment = 60 d*	*87*	*96*	*61*	
61790-31-6				***73% ThOD in 28 d***				

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution [a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Acute Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory I: Substituted Amides (continued)								
124-26-5	k_{phot} = 27 E-12 $t_{1/2}$ = 9.5 hr	NC	air: < 1% water: 13% soil: < 1% sediment: 87%	$t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 60 d	not toxic at solubility	not toxic at solubility	0.0004	
110-30-5	k_{phot} = 70 E-12 $t_{1/2}$ = 3.6 hr	NC	air: < 1% water: 5% soil: < 1% sediment: 95%	$t_{1/2}$ water = 37.5 d $t_{1/2}$ soil = 37.5 d $t_{1/2}$ sediment = 150 d	not toxic at solubility	not toxic at solubility	not toxic at solubility	
68140-00-1				**92% DOC**	**31**	**38**	**E_bC_{50} = 1.1** [b]	

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Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.

[b] E_bC_{50} is the EC_{50} based on growth (biomass); E_rC_{50} is the EC_{50} based on growth rate.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution [a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Acute Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory I: Substituted Amides (continued)								
68603-42-9				**84% ThOD in 28 d; 61 - 93% degradation in 14 d [c]; 51.8% ThOD in 28 d**	**6.7**	**3.3 2.15 [d] 2.64 [d]**		
68140-01-2								
301-02-0	k_{phot} = 80 to 88 E-12 $t_{1/2}$ = 3.0 to 3.2 hr	NC	air: < 1% water: 14% soil: < 1% sediment: 86%	**80% ThOD in 28 d** $t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 60 d	not toxic at solubility	not toxic at solubility	0.0004	
93-83-4	k_{phot} = 111 to 118 E-12 $t_{1/2}$ = 2.2 to 2.4 hr	NC	air: < 1% water: 34% soil: < 1% sediment: 66%	$t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 60 d	**2.6** not toxic at solubility	not toxic at solubility	not toxic at solubility	

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.
[c] Several techniques were evaluated. Data range indicates different values from the various procedures.
[d] Replicate values from the same study.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution[a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Acute Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory I: Substituted Amides (continued)								
68155-20-4								
68425-47-8								
112-84-5	k_{phot} = 86 to 93 E-12 $t_{1/2}$ = 2.8 to 3.0 hr	NC	air: < 1% water: 5% soil: < 1% sediment: 95%	**15 and 43% ThOD in 28 and 140 d, respectively; 28% ThOD in 28 d** $t_{1/2}$ water = 37.5 d $t_{1/2}$ soil = 37.5 d $t_{1/2}$ sediment = 150 d	**NOEC > 0.105 mg/l (28 days)** not toxic at solubility	not toxic at solubility	not toxic at solubility	**NOEC = 0.080**
Subcategory II – Fatty Acid Reaction Products with Amino Compounds								
68131-13-5								
8051-30-7								
61790-63-4								

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution[a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Acute Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory II – Fatty Acid Reaction Products with Amino Compounds (continued)								
61790-69-0								
68132-46-7								
68910-93-0				**30 - 40% ThOD in 126 d**	**0.43**			
64754-93-4								
68910-87-2								
68953-36-6								
71820-35-4						**0.30**		
Subcategory III – Imidazole Derivatives								
68122-86-1				**5% BOD in 20 d**	**59**			
61791-39-7						**1.5**		
68442-97-7								
72623-72-4								
72749-55-4								
65817-50-7								

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution[a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Acute Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory IV – FND Amphoterics								
693-33-4	k_{phot} = 40 E-12 $t_{1/2}$ = 6.4 hr	NC	air: < 1% water: > 99% soil: < 1% sediment: 0.5%	$t_{1/2}$ water = 15 d $t_{1/2}$ soil = 15 d $t_{1/2}$ sediment = 60 d	0.15	**2.5** 0.15	0.0004	
4292-10-8				**82% ThOD in 28 d**			**NOEC = 100**	
61789-39-7					**0.23**			

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.

Table 3 (continued)

Environmental Fate and Ecotoxicity Data for FND Amides Chemical Category

CAS RN	Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution [a]	Biodegradation	Acute/Prolonged Tox. to Fish LC_{50} (mg/l)	Acute Tox. to Invertebrates EC_{50} (mg/l)	Acute Toxicity to Aquatic Plants EC_{50} (mg/l)	Chronic Tox. to Aquatic Invertebrates EC_{50} (mg/l)
Subcategory IV – FND Amphoterics (continued)								
61789-40-0				**97% DOC removed (3 h hydraulic retention time); 71% $ThCO_2$ in 35 d; ≥ 93% $ThCO_2$ in 28 d; ≈ 100% DOC in 28 d; ≈ 100% DOC in 28 d; 86% degraded in 28 d; Anaerobic - ≈ 56% degraded in 56 d**	**2.0 2.0 6.73 NOEC = 0.16 (28 d)**	**21.5 6.40 1.1 NOEC = 0.9 (21 d)**	**E_bC_{50} = 30 [b] and E_rC_{50} = 48; EC_{50} = 0.55; EC_{50} = 0.55; NOEC = 0.96 (72 hr)**	
70851-07-9				***> 90% degraded in 13 d***				

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.
NC = Not calculable for FND Amides with the HYDROWIN submodel.

[a] Water was assumed to be the primary route of entry into the environment.

[b] E_bC_{50} is the EC_{50} based on growth (biomass); E_rC_{50} is the EC_{50} based on growth rate.

Table 4

Human Health-Related Data for FND Amides Chemical Category

CAS RN	Acute Oral Toxicity LD_{50} (g/kg)	Acute Inhalation Toxicity	Acute Dermal Toxicity LD_{50} (g/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)
Subcategory I: Substituted Amides							
142-78-9					**Not mutagenic (Ames)**		
120-40-1	**> 3.5; > 5 ml/kg**		**> 2**	**50** [a]	**Not mutagenic (Ames)**	**> 1000** [a]	[b]
68155-06-6	***> 10 (Males)***				***Not mutagenic (Ames)***		[c]
61790-31-6	***> 5***						
124-26-5	**> 10**				**Not mutagenic (Ames)**		
110-30-5		**At 112 mg/m^3 no deaths and mild and transient inflammatory response in the lung**			**Not mutagenic (Ames)**		

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
Empty block denotes data either are not available or are available and judged inadequate.

[a] 90-day rat oral feeding study; histological evaluation of reproductive organs is adequate for SIDS reproductive screening. Toxicity to reproduction evaluation shown in robust summary for repeated dose toxicity.

[b] Data for CAS RN 68603-42-9 are appropriate since CAS RN 120-40-1 is a major component (44 – 53%).

[c] CAS RNs 68155-06-6 (C12 - C18) and 68603-42-9 (C8 - 16) are very similar and the developmental toxicity study is considered to represent both compounds.

Table 4 (continued)

Human Health-Related Data for FND Amides Chemical Category

CAS RN	Acute Oral Toxicity LD_{50} (g/kg)	Acute Inhalation Toxicity	Acute Dermal Toxicity LD_{50} (g/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)
Subcategory I: Substituted Amides (continued)							
68140-00-1	**> 5; 7.4; > 5 [d]; > 5 ml/kg**		**> 2**	**> 750 [a]**	**Not mutagenic (Ames)**	**> 750 [a]**	
68603-42-9	**> 5; > 5; > 5**		**> 2**				**Rat maternal and developmental > 1000 [b]**
68140-01-2							
301-02-0	**12.4 ml/kg**				**Not mutagenic (Ames)**		
93-83-4							
68155-20-4		**Sensory and pulmonary irritant at 86 to 219 mg/m^3**					
68425-47-8							
112-84-5	**> 5**			**7500 [c]**	**Not mutagenic (Ames)**		

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
Empty block denotes data either are not available or are available and judged inadequate.

[a] 90-day rat oral feeding study; histological evaluation of reproductive organs is adequate for SIDS reproductive screening. (Toxicity to reproduction evaluation shown in robust summary for repeated dose toxicity.)

[b] CAS RNs 68155-06-6 (C12 - C18) and 68603-42-9 (C8 - 16) are very similar and the developmental toxicity study is considered to represent both compounds.

[c] Animals dosed (gavage) 10 times a day for five days followed by a post-dose period of 23 days.

[d] The LD_{50} of the original solution (10%) was > 50 ml/kg

Table 4 (continued)

Human Health-Related Data for FND Amides Chemical Category

CAS RN	Acute Oral Toxicity LD_{50} (g/kg)	Acute Inhalation Toxicity	Acute Dermal Toxicity LD_{50} (g/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)
Subcategory II – Fatty Acid Reaction Products with Amino Compounds							
68131-13-5							
8051-30-7							
61790-63-4							
61790-69-0							
68132-46-7							
68910-93-0							
64754-93-4							
68910-87-2					***Not mutagenic (Ames)***		
68953-36-6							
71820-35-4	**3.61 (Male) 4.26 (Female); > 5**				**Not mutagenic (Ames – 2 studies)**		

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
CAS RN and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.

Table 4 (continued)

Human Health-Related Data for FND Amides Chemical Category

CAS RN	Acute Oral Toxicity LD_{50} (g/kg)	Acute Inhalation Toxicity	Acute Dermal Toxicity LD_{50} (g/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)
Subcategory III – Imidazole Derivatives							
68122-86-1	**> 5; 8.45 ml/kg**			**143** [e] **> 2200** [f]	**Not Mutagenic (Ames); CHO Cyto-genetics (Neg); UDS (Neg)**	**> 1322** [g]	**Maternal and developmental > 1000** [h]
61791-39-7							
68442-97-7	**< 5 (60% died at 5 g/kg)**						
72623-72-4							
72749-55-4							
65817-50-7							
Subcategory IV – FND Amphoterics							
693-33-4							**Maternal = 50 Developmental = 150** [i]
4292-10-8							

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
Chemicals and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.

[e] 13-week dietary toxicity study in dogs.

[f] 91-day feeding study in rats

[g] Evaluation of reproductive organs from the 13-week oral feeding study in dogs adequate for SIDS/HPV reproductive screening (included in Robust Summary for 13-week study).

[h] Developmental toxicity study in rats. A probe study conducted prior to the definitive study indicated no maternal or fetal toxicity at the highest dose of 1875 mg/kg/day (see Robust Summary in Appendix A).

[i] Dose selection study is included as a Robust Summary in Appendix A.

Table 4 (continued)

Human Health-Related Data for FND Amides Chemical Category

CAS RN	Acute Oral Toxicity LD_{50} (g/kg)	Acute Inhalation Toxicity	Acute Dermal Toxicity LD_{50} (g/kg)	Repeated Dose Toxicity NOAEL (mg/kg/day)	Genetic Toxicity	Toxicity to Reproduction NOAEL (mg/kg/day)	Developmental Toxicity NOAEL (mg/kg/day)
Subcategory IV – FND Amphoterics (continued)							
61789-39-7							
61789-40-0	**> 1.8 (Males) [j]** **2.6 [k]** **1.5 [l]** **> 1.5 g/kg [m]**		**> 2 g/kg [n]**	**250 [o]** **500 [p]** **LOAEL = 300**	**Not Mutagenic (Ames – 4 studies);** ***In vivo* Mouse Micro-nucleus – (Neg)**	**> 1000 [o]** **> 1000 [p]**	
70851-07-9							

Note: Bold print indicates reliable data for which a Robust Summary is provided in Appendix A.
Regular font indicates data obtained from appropriate models as described in the text.
Chemicals and data in italics are for supporting chemicals [non-HPV].
Empty block denotes data either are not available or are available and judged inadequate.

[j] Value is in ml/kg of a 35.6% aqueous solution; none of 5 males died, all 5 females died; therefore, an LD_{50} for females was not established. (See Robust Summary 74, Appendix A)

[k] LD_{50} of the original solution (30% aqueous) was 8.55 g/kg

[l] LD_{50} of the original solution (30% aqueous) was 4.9 g/kg.

[m] Study was conducted with 5 g/kg of a solution containing 31% active ingredient.

[n] Acute dermal toxicity study in rats.

[o] 90-day rat oral gavage study; histological evaluation of reproductive organs is adequate for SIDS reproductive screening. (Toxicity to reproduction evaluation shown in robust summary for repeated dose toxicity.)

[p] 28-day rat oral gavage study; histological evaluation of reproductive organs is adequate for SIDS reproductive screening. (Toxicity to reproduction evaluation shown in robust summary for repeated dose toxicity.) A range-finding study (Appendix A) was also reviewed with a LOAEL determined to be 300 mg/kg/day based on clinical signs.